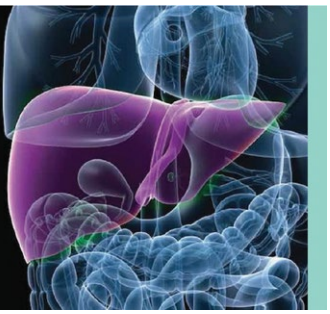

When the Creation of a Consortium Provides Useful Answers: Experience of The Latin American DILI Network (LATINDILIN)

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Abbreviations: ALEH, Asociación Latinoamericana para el Estudio del Hígado; DILI, drug-induced liver injury; INH, isoniazid; LATINDILIN, Latin American DILI Network; NSAID, nonsteroidal anti-inflammatory drug; PIZ, pyrazinamide; RIP, rifampicin.

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Potential conflict of interest: Nothing to report.

Received August 28, 2018; accepted October 29, 2018.

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Drug-induced liver injury (DILI) represents an unsettled issue because of the fact that roughly 1000 drugs have been involved in liver damage[1] and hepatotoxicity can mimic all forms of acute and chronic liver disease. Although most DILI episodes are self-limited with resolution after withdrawal of the culprit agent, hepatotoxicity is the most common cause of acute liver failure in several countries.[2]

DILI has been traditionally classified in predictable (dose-related) or unpredictable (not dose-related) mechanisms. Unpredictable reactions are also described as idiosyncratic, either immune-mediated hypersensitivity or nonimmune reactions.[2]

DILI diagnosis is still a challenging issue in clinical practice and depends on exclusion of other causes. Physicians faced with abnormal liver enzymes in the absence of other more common hepatic diseases should always have a high level of suspicion. Polypharmacy and underlying liver diseases can further complicate DILI assessment. The liver-specific CIOMS/RUCAM (Council for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method) scale, albeit imperfect, is still the best scoring system for causality assessment.[3] Clinicians have to keep in mind that an accurate pharmacological history stretching at least 6 months prior to DILI onset, encompassing herbal and dietary supplements, as well as over-the-counter medications, should always be obtained when assessing DILI.

The Latin American DILI Network (LATINDILIN) is a recently established consortium of Latin American–based hepatologists intended to foster the identification and characterization of DILI cases in Central and South America.[4] The rationale behind establishing a network to prospectively identify DILI cases in this geographical region, aside from improving Latin American-based hepatologists' skills and awareness of DILI, is the feeling that genetic background, including race and ethnicity, prescription policies, and the use of ancestral herbal remedies, among other factors, may account for a particular landscape of clinical presentation and outcomes of this liver disorder when compared with other parts of the world. In this review, we will describe and discuss the goals and achievements of this initiative.

RATIONALE BEHIND THE CREATION OF THE LATINDILIN

DILI is an uncommon liver reaction characterized by a wide range of phenotypic presentations and several degrees of severity, where diagnosis is still based on clinical and biochemical variables that qualify the case for liver injury and exclude alternative causative factors while awaiting the development of sensitive and specific biomarkers to the early diagnosis of hepatotoxicity.

Despite the fact that there are no standard guidelines and recommendations on how to design and create a registry, these networks use an observational methodology to collect data from patients. This structure not only allows networks to conduct epidemiological studies, but also to carry out several other kinds of studies, such as clinical trials, natural history, and quality-of-life investigations.[5]

In this scenario, the creation of prospective DILI registries, which allow the characterization of cases with sufficient follow-up to ascertain outcomes, becomes a very valuable tool to study the epidemiology, phenotypic presentation, and risk factors related to the main culprit drugs or herbs and dietary supplements in clinical practice.

Data on patients with DILI in Latin America have been historically scarce, usually coming from case reports or small series of patients[6] because there was no specific structure that could allow tackling these scientific challenges in an efficient and collaborative way. With this perspective in mind, the LATINDILIN initiative set up a network of hepatologists working on the same structured protocol to collect relevant information and to establish causality with confidence.

In addition, it was of interest to assess how the differences in patterns of drug prescriptions, the frequent use of traditional remedies, the practice of self-medication along with diverse pharmaceutical policies, or heterogeneity in ethnicities could influence the susceptibility to DILI.

This project was supported by the University of Málaga and the Spanish DILI Registry, created in 1994, which already had exhibited extensive experience in the field of hepatotoxicity.[7,8]

The LATINDILIN was set up in 2011[4] to prospectively identify DILI cases and to build up a collection of biological samples to further study the underlying mechanisms of DILI, and from the beginning, it joined existing DILI consortiums in efforts to identify genetic markers of susceptibility. Representatives from several Latin American countries, including Argentina, Uruguay, Chile, Brazil, Peru, Mexico, Paraguay, Ecuador, Venezuela, and the Dominican

Republic, increasingly incorporated to the network and were committed to this project.

IMPLEMENTATION AND STRATEGIC OPERATIVE STRUCTURE OF THE LATINDILIN

To meet our goals, we had to implement both a specific dynamic and an orderly work scheme. First, after protocol approval by the local ethical review board, the physicians contacted and committed to the project are responsible for spreading it in their respective countries and for generating, by using the resources most suitable to their local situations, an internal training network for possible DILI cases.

Based on the suspicion of DILI and having the patient's informed consent following the Spanish model, the clinician in charge fills out a standardized form that is sent to the coordinating physician in each country for a first evaluation and then to the coordinating center in Málaga, Spain, to ascertain causality.[9]

Once in the coordinating center, the information provided in the protocol form is analyzed for completeness, and the possible association with the drug and potential for drug-drug interactions are evaluated. Three independent experts analyze and discuss the alternative etiologies that were excluded, and, finally, the event is either adjudicated or not as DILI (Fig. 1).

Notably, the Asociación Latinoamericana para el Estudio del Hígado (ALEH; Latin American Association for the Study of the Liver) has supported and fostered this project since its conception and provided the group with a prominent place on its website (http://www.alehlatam.org).

ACHIEVEMENTS AND HURDLES IN THE DEVELOPMENT OF THE LATIN DILI NETWORK

Several achievements have been attained to date. The first achievement is that this registry has contributed to increasing the knowledge and awareness of this intriguing disorder in Latin America.

By following the methodology described earlier, 330 well-vetted DILI cases have been recruited from different Latin American countries as shown in Fig. 2. Of 311

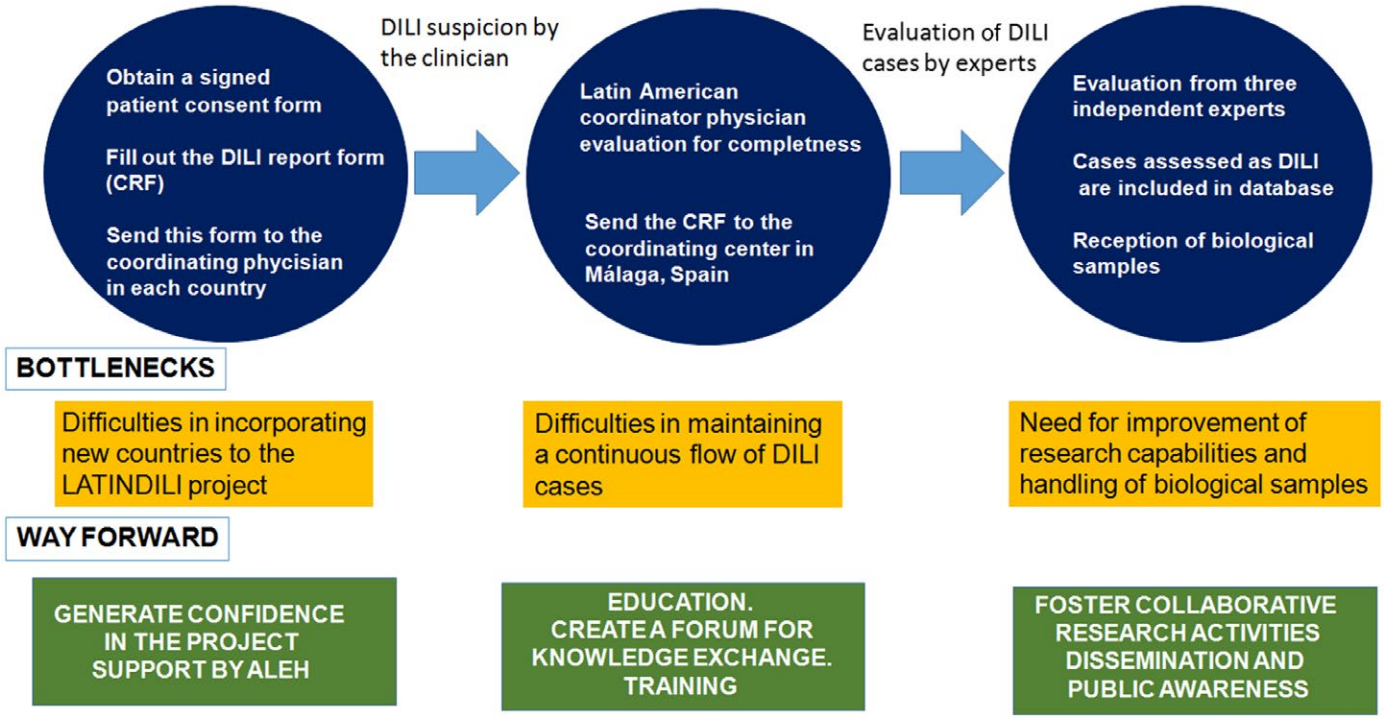

FIG 1 Schema for DILI cases enrollment in the LATINDILIN.

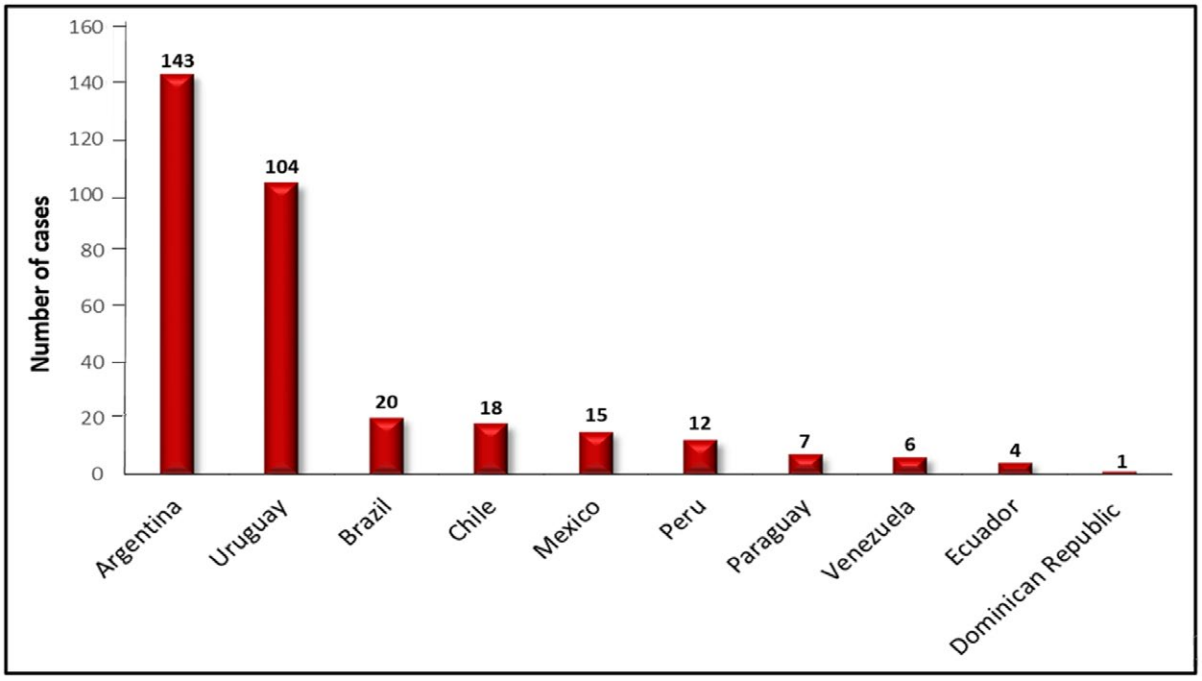

FIG 2 Number of DILI cases submitted at the LATINDILIN by country.

patients assessed in LATINDILIN, the average age was 50 years (11-91 years), and 61% were female.

Hepatocellular type of injury was observed in 60% of the cases, whereas cholestatic liver damage was documented in 25% (Table 1). The comparison of demographics and clinical parameters with the data obtained from the cases included in the Spanish DILI Registry showed significant female sex predominance, longer duration of therapy, and longer time to onset of symptoms in the Latin American registry.

These differences may be explained by changes in prescription habits among continents. As an example, nitrofurantoin-induced DILI showed more prevalence in Latin America compared with the Spanish network, probably linked to a long-term prophylaxis prescription (months to years) of recurrent urinary infections commonly indicated in Latin American countries, unlike in Spain where nitrofurantoin is prescribed for only short periods not exceeding 2 weeks.

Also, there were noticeable differences among pharmacological groups of drugs between registries. Anti-infectives (32%), musculoskeletal agents (14%), antineoplastics (8.6%), sex hormones (8.2%), and central nervous system

TABLE 1. COMPARISON OF DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF DILI CASES WITH A SINGLE EPISODE INCLUDED IN THE LATINDILIN AND THE SPANISH DILI REGISTRY

Variables	LATINDILIN (N = 311)	Spanish DILI Registry (N = 878)	*P* Values
Age (years), mean (range)	50 (11-91)	54 (14-89)	0.474
Female sex, %	61	47	<0.01
DILI episode			
Jaundice, %	64	68	0.25
Duration therapy (days)			0.021
Mean ± SD	119 ± 342	88 ± 224	
Median	35	27	
Time to onset (days)			0.043
Mean ± SD	104 ± 324	80 ± 216	
Median	31	25	
Pattern of liver injury, %			0.087
Hepatocellular	60	64	
Cholestatic	25	19	
Mixed	15	17	
nHy's law, n (%)	112 (36)	355 (40)	0.252
Severity, n (%)			0.328
Mild	96 (33)	256 (30)	
Moderate	155 (53)	503 (59)	
Severe	26 (8.9)	61 (7.1)	
Fatal	15 (4.9)	34 (4)	

drugs (8.2%) were the most commonly involved therapeutic groups in the LATINDILIN, whereas in the Spanish DILI Registry, anti-infectives (38%), central nervous system drugs (13%), musculoskeletal agents (11%), and cardiovascular drugs (10%) were the most represented. Amoxicillin-clavulanate ranked first in the LATINDILIN, Spanish DILI, and DILI Network registries,[10] whereas antituberculous drugs were the most prevalent culprit agents in the Indian network.[11] There were also striking differences among the list of main culprit DILI drugs across the different registries that could be explained by differences in disease prevalence and patterns of drug use (Table 2).

The second achievement is that, through the establishment of standardized prospective data collection procedures and sample sharing, this registry has enabled delineation of the distinct profile of hepatotoxicity in Latin America caused by specific drugs or herbal and dietary supplements mainly used in this continent, for example, the first description of severe immunological liver damage induced by cyproterone acetate,[12] the analysis of DILI risk induced by coxibs in clinical practice,[13] or the compilation of one of the largest series of nitrofurantoin hepatotoxicity.[14]

In addition, LATINDILIN, together with the Spanish DILI Registry, has contributed to developing an understanding of a drug's hepatotoxicity, identifying a cholestatic phenotype associated with renal damage in patients illicitly taking anabolic steroids.[15]

A total of 110 of 311 (36%) cases included in the LATINDILIN registry met the new Hy's law criteria (see Table 1). An improved Hy's law definition (nHy's law) and a composite algorithm for early prediction of drug-induced acute liver failure were proposed by Robles-Diaz et al.[16] analyzing cases recruited by the Spanish DILI Registry and validated in the Latin American cohort.

Although nonsteroidal anti-inflammatory drugs (NSAIDs) account for an important fraction of DILI cases in the LATINDILIN registry, the specific NSAIDs responsible clearly differ between the two registries, with diclofenac the top agent in Latin America and ibuprofen in the Spanish DILI Registry.[9] Twenty-one ibuprofen-induced idiosyncratic hepatotoxicity cases from the Spanish DILI Registry and five cases included in the LATINDILIN have been reported. Ibuprofen was the most frequent causative drug (29%), followed by diclofenac (18%), among the 73 NSAID DILI cases in the Spanish DILI Registry. Hepatocellular injury was the most frequent clinical pattern at presentation, and 12% of these patients experienced severe liver disease or received liver transplant.[17]

Finally, through our collaboration with the International Drug-Induced Liver Injury Consortium, we have contributed to collaborative international genome-wide association studies as a strategy to identify the genetic variations that increase the susceptibility to DILI.[18]

However, this pathway to collaborative research has obviously found hurdles in its implementation, as there has

TABLE 2. TOP 10 INDIVIDUAL AGENTS THAT CAUSE DILI IN THE LATINDILI NETWORK COMPARISONS AMONG THE SPANISH DILI REGISTRY, DILI NETWORK, AND PUBLISHED INDIAN DILI COHORT

Agent	LATINDILI Network (N = 311)	Spanish DILI Registry (N = 878)	Chalasani et al. (2015)[10] (DILI Network) (N = 899)	Devarbhavi et al.[11] (India) (N = 313)
Amoxicillin-clavulanate	41	202	91	3
Nitrofurantoin	19	2	42	—
Diclofenac	18	16	12	1
RIP + INH + PIZ	12	28	—*	181†
Nimesulide	12	9	—‡	2
Ibuprofen	9	27	1	2
Cyproterone	9	3	—	—
Carbamazepine	8	8	4	9
Methyldopa	6	0	11	0
Atorvastatin	5	18	8	5

*Rifampicin (RIP), isoniazid (INH), and pyrazinamide (PIZ) are taken together. Forty-eight cases were adjudicated to INH, two cases were adjudicated to RIP, and two were adjudicated to PIZ in the DILI Network.

†Described as antituberculous drugs and consist of RIP + INH + PIZ + ethambutol.

‡Nimesulide is not marketed in the United States.

TABLE 3. FUTURE PERSPECTIVES AND CLINICAL IMPACT OF THE LATINDILIN

Expected Actions	Clinical Utility
Maintenance of a large database of well-vetted DILI cases	To improve diagnostic algorithm scales; identify risk factors and outcomes
Physician awareness of DILI and patients as direct beneficiaries of this network	To enhance early diagnosis; to support clinicians in the management decision-making processes and counseling of patients
Detection or amplification of "liver safety signals"	To foster a close collaboration with the regulatory agencies; impact on public health and drug development
Better understanding of underlying mechanisms in DILI	To enroll new centers and improve their capacity for research activities and biological samples collection
Optimization of the training capacities related to DILI	To set up a special interest group in DILI at ALEH to establish effective channels of communication and to facilitate exchange programs
Fostering of hypothesis-driven research in DILI	To design multicenter clinical trials to assess the efficacy of new therapeutic agents in DILI
	To participate in studies for biomarkers qualification
	To increase the scientific output to gain in visibility

been the need to create a new pharmacoepidemiological culture among physicians and let them think about drugs as a cause of liver disease. The way to move forward and make a difference is to shift from the traditional way of working, centered on one's own group, to a new paradigm where networks and alliances with national and international groups are established. To overcome the roadblocks to success, we have tried to generate confidence and trust among all partners, to facilitate spaces for exchange of ideas and problem-solving solutions in a transparent and reliable way, and to foster research activities and participation in short-term scientific missions. Publications made by the consortium have proved to be a unique way to empower the main actors and inspire the younger physicians (Fig. 1).

FUTURE PROSPECTS

The LATINDILIN registry is still a young network but has managed to consolidate itself as a working group and is positioning in the specialized international community due to its rigorous performance and scientific validity. With the experience gathered throughout these years, we believe that attention should be focused on education and training to improve the diagnostic skills to foster research and innovation and the participation in global collaborative initiatives to advance the safety of drugs. A description of the future perspectives and clinical impact of DILI registries is given in Table 3.

In brief, the future challenges of our LATINDILIN are as follows:

1. To characterize the signature of the most frequently involved drugs in DILI, the host and drug risk factor modifiers, and outcome in this population.
2. To make physicians fully aware of this distinct disease to enhance its early diagnosis and management and to be able to counsel patients on future treatments and outcome, as patients are direct beneficiaries of these networks.
3. To foster a closer collaboration with the regulatory agencies so that detected safety signals can be managed in a comprehensive manner.
4. To design and facilitate the conduct of multicenter clinical trials to assess the effect of new therapeutic agents potentially useful in idiosyncratic DILI
5. To participate in studies for qualification of biomarkers and other international joint activities to get a deeper understanding of DILI

Altogether, to maintain the ongoing project and keep the flame burning, we need the spark of enthusiasm of dedicated physicians and researchers, the willingness to cooperate in a timely fashion, and most of all, funding.

CORRESPONDENCE

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